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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/768,953

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Amedeo Leonardi

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EXAMINER

ROYDS, LESLIE A

ART UNIT

PAPER NUMBER

1614

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/768,953	<b>Applicant(s)</b> LEONARDI ET AL.	
	<b>Examiner</b> Leslie A. Royds	<b>Art Unit</b> 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 February 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1, 11-18, 20 and 28-30 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 11-18, 20 and 28-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

**Applicant is notified that the finality of the previous Office Action dated June 14, 2007 is hereby withdrawn. The after-final amendment filed February 12, 2008 has been entered into the record and prosecution of the present application has been reopened.**

Applicant's after-final amendment filed February 12, 2008 has been received and entered into the instant application. Claims 1, 11-18, 20 and 28-30 are pending. Claims 2-10, 19, 21-27 and 31-58 are cancelled and claims 1, 11-18, 20 and 29 are amended.

Applicant's arguments and amendments, filed February 12, 2008, have been fully considered. Regrettably, however, the allowability of the instant claims is hereby withdrawn upon reconsideration of the present claim set and the prior art. Accordingly, the following rejection is newly applied and constitutes the complete set of rejections applied to the instant claims.

#### ***Claim Rejections - 35 USC § 103 (New Grounds of Rejection)***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 1, 11-18, 20 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cosford et al. (WO 2001/16121, 2001; cited by Applicant) in view of Bonney et al. ("Bladder Dysfunction in Schizophrenia", *Schizophrenia Research*, 25(1997):243-249) and Nilvebrant ("Clinical Experiences with Tolterodine", *Life Sciences*, 68(2001):2549-2556; cited by Applicant), each already of record.

Cosford et al. teach compounds of the formula A-L-B, defined at p.19-20, of which the species 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (Example 169, p.100) is expressly exemplified and is identical to Applicant's elected species of "MTEP" (see present claim 1), useful for therapeutic applications, such as, *inter alia*, the treatment of schizophrenia (p.21, l.1-9), comprising the administration of a therapeutically effective amount of at least one of the disclosed heterocyclic compounds to a patient having a disease (p.22, l.26-29). Cosford et al. further teach that the disclosed compositions may be administered to a patient using oral, sublingual, intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraocular, intracranial, inhalation, rectal or vaginal methods (p.23, l.14-17) and may further be compounded with non-toxic, pharmaceutically acceptable carriers (p.23, l.19-22), such as, but not limited to, sterile water, sterile saline, propylene glycols, polyethylene glycols, vegetable oils, etc. (p.24, l.4-15). Cosford et al. additionally discloses dosage amounts typically in the range of about 0.001-100 mg/kg/day (p.25, l.19-21), but further teaches that the specific therapeutically effective dose level for a particular patient will depend upon a variety of factors, e.g., the disorder being treated, severity of disease, age, sex, etc. (p.25, l.11-19).

Here, though Cosford et al. teaches 0.001-100 mg/kg/day dose level and not a total daily dose, it would have been obvious that for an average 70 kg adult human, such a dose range would constitute daily dosage amounts of 0.07-7000 mg/day, which overlaps the dosage amounts presently claimed in present claims 16-18. In light of such, it is clear that the art recognized the administration of the claimed

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compound in amounts encompassing or overlapping those amounts presently claimed and, thus, the use of such a compound in amounts such as those presently claimed would have naturally commended themselves, and would have been *prima facie* obvious, to one of ordinary skill in the art. In addition, the concentration of the active ingredient is a result-effective variable, i.e., a variable that achieves a recognized result, and, therefore, the determination of the optimum of workable dosage range would be well within the practice of routine experimentation by the skilled artisan, absent factual evidence to the contrary, and, further, absent any evidence demonstrating a patentable difference between the compositions used and the criticality of the amount(s).

Cosford et al. fails to specifically teach the treatment of patients in need of treatment of urinary incontinence (claim 1) or the concomitant use of an antimuscarinic agent, such as oxybutynin, tolterodine, darifenacin or temiverine (claims 1 and 20).

Bonney et al. teaches that studies of schizophrenic patients have demonstrated particular anatomical lesions, such as ventricular enlargement (hydrocephalus), selective neuronal loss with gliosis and dopamine dysregulation that have been proposed to interrupt the pathway of bladder control or cause neurotransmitter dysfunction (paragraph bridging pages 243-244). Bonney et al. teaches that many schizophrenic patients have brain abnormalities that are similar to those associated with urge incontinence and detrusor hyperreflexia in neurological patients and proposes that bladder dysfunction and incontinence are neurobiological correlates of schizophrenia (abstract). Bonney et al. further discloses that incontinence was clearly associated with a diagnosis of schizophrenia, as evidenced by the percentage of schizophrenic patients with incontinence (i.e., 37%, see page 246, Table 2) versus patients with other mood disorders (i.e., 18%, see page 246, Table 2).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed compound(s) of Cosford et al. would have been reasonably expected to exert the same or substantially similar efficacy in the treatment of urinary

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incontinence because: (1) the compound(s) of Cosford et al. were known to have efficacy in treating schizophrenic patients, (2) a significant proportion of schizophrenic patients also experience concomitant urinary urge incontinence as taught by Bonney et al., and (3) the urinary incontinence commonly seen in schizophrenic patients is considered to be correlated to and, i.e., result from, the brain abnormalities that are characteristic of schizophrenia, as also taught by Bonney et al. Cosford provides the clear teaching that the instantly claimed compound (i.e., "MTEP") is, in fact, effective for treating all schizophrenic patients, i.e., 100% of schizophrenics, without exclusion. Of this entire schizophrenic population, Bonney provides the factual extrinsic evidence demonstrating that a subpopulation of schizophrenic patients also suffers concomitantly from urge incontinence. Accordingly, the suggestion of Cosford to use the claimed MTEP compound for treating any schizophrenic is a clear suggestion to use it in any subpopulation of schizophrenic patients, such as those patients also suffering from urge incontinence, with the reasonable expectation of the same (or at least substantially similar) level of efficacy in treating this subpopulation of patients as would be expected in the treatment of schizophrenic patients per se. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed MTEP compound has in treating urinary incontinence must necessarily be present in the method disclosed by Cosford et al., absent factual evidence to the contrary.

Further, regarding the concomitant use of an antimuscarinic drug with the MTEP compound as presently claimed (claims 1 and 20), Nilvebrandt teaches tolterodine as a non-selective muscarinic receptor antagonist for the treatment of overactive bladder that has a greater effect on the bladder than on the salivary glands *in vivo*, which improves the tolerability of the compound by decreasing the incidence of dry mouth (abstract). Nilvebrandt further teaches that the efficacy of tolterodine in treating overactive bladder is equal to that of oxybutynin, but with significantly enhanced tolerability (abstract). Nilvebrandt quantifies the activity of tolterodine versus oxybutynin in treating episodes of urinary incontinence at

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Figure 2(A), which shows tolterodine to have substantially similar inhibitory activity to that of oxybutynin (page 2552).

One of ordinary skill in the art would have been motivated to combine the pharmaceutical composition of Cosford et al., which comprises the compound 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine, with the muscarinic receptor antagonist tolterodine as taught by Nilvebrandt because Bonney provides a clear teaching that a subpopulation of schizophrenic patients also suffers concomitantly from urge incontinence. In view of such teachings, the use of a multivalent therapy comprising an effective anti-schizophrenic agent (i.e., in this case, MTEP) in combination with an effective overactive bladder-treating agent would have been *prima facie* obvious to one of ordinary skill in the art treating patients suffering from schizophrenia. Such a person would have been motivated to do so not only to provide the schizophrenic patient with an effective schizophrenia-ameliorating pharmaceutical agent (i.e., MTEP), but also to provide this particular subpopulation of schizophrenics that concomitantly suffer from urinary incontinence an effective pharmacologic means of treating this urinary dysfunction via using a known overactive bladder-treating agent, such as the antimuscarinic agent tolterodine, as evidenced by Nilvebrandt. This is because it is generally *prima facie* obvious to use, in combination, two or more agents to treat multiple symptoms resulting from the same condition in order to provide a means of ameliorating the medical condition that triggered such symptoms, and further thereby improving the patient's overall health.

### ***Conclusion***

Rejection of claims 1, 11-18, 20 and 28-30 is proper.

No claims of the present application are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/  
Patent Examiner, Art Unit 1614

March 26, 2008

/Ardin Marschel/  
Supervisory Patent Examiner, Art Unit 1614